PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Applicant's or agent's file reference see form PCT/ISA/220	Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet) **FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2005/000007	05.01.2005	05.01.2004

International Patent Classification (IPC) or both national classification and IPC
C12N15/62, A61K47/48, C07K14/54, C07K16/30, A61P35/00

Applicant
EMD LEXIGEN RESEARCH CENTER CORP.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2005/000007

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☒ furnished subsequently to this Authority for the purposes of search.

3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 51-52, and part of 47

because:

☒ the said international application, or the said claims Nos. 47 in part relate to the following subject matter which does not require an international preliminary examination *(specify)*:
see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 51-52

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

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Box No. IV Lack of unity of invention

1. ☐ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ not paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-50

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-33, 35-50
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-50
Industrial applicability (IA)	Yes:	Claims	1-46,48-50
	No:	Claims	47

2. Citations and explanations

   see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 51 and 52 do not contain any technical features which allow for a search to be performed. The following is limited accordingly.

Claim 47 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item IV

Lack of unity of invention

The problem underlying the present application is, to provide an effective medicament for treating solid tumours.
As solution to this problem, several proteins are proposed, in which (part of) interleukin-12 (IL-12) is fused to (part of) an antibody, which targets oncofoetal fibronectin.
The technical feature, linking these solutions together, is the combination of both these features in one single fusion protein, used in the treatment of solid tumours.

However, three documents disclose a fusion protein of anti-oncofoetal fibronectin with IL-12, and its efficacy in the treatment of tumours:
CANCER RESEARCH, vol. 63, no. 12, 15 June 2003 (2003-06-15), pages 3202-3210, ISSN: 0008-5472
CANCER RESEARCH, vol. 63, no. 5, 1 March 2003 (2003-03-01), pages 1144-1147, ISSN: 0008-5472
and
NATURE BIOTECHNOLOGY, vol. 20, no. 3, March 2002 (2002-03), pages 264-269, ISSN: 1087-0156
This conjugate seems excluded in claims 1-33, but not in claim 34.
Moreover, in **WO 03/093478 A**, on page 26, line 24 of the table, the combination IL-12 + anti-oncofetal fibronectin is mentioned as one of the preferred combinations.

For this reason, the technical feature mentioned above can no longer be accepted as special technical feature linking the different inventions together. Since there is no other technical feature that could fulfil the role of special technical feature in the sense of Rule 13.2 PCT, the present application is found to lack unity of invention, containing the subjects mentioned below.

No.	Claims	Subject
1	1-34, 43-50	Compound containing of a portion targeting oncofoetal fibronectin and IL-12 as effector portion, pharmaceutical composition containing it, and its use in the treatment of cancer, according to these claims.
2	35-39	Nucleic acid encoding the fusion protein of anti-oncofoetal fibronectin and IL-12, or encoding part of it.
3	40-42	Expression vector as claimed, host cell as claimed, and their use in the method of making a compound as claimed

Nevertheless, as the search for each of these subjects seemed complete, and as the reasoning for each of these inventions is based on similar considerations, the present authority decided not to ask for further fees.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Reference is made to the following documents:

D1: HALIN CORNELIA ET AL: "Synergistic therapeutic effects of a tumor targeting antibody fragment, fused to interleukin 12 and to tumor necrosis factor alpha." CANCER RESEARCH, vol. 63, no. 12, 15 June 2003 (2003-06-15), pages 3202-3210, XP002342601 ISSN: 0008-5472

D2: THORPE P E ET AL: "The First International Conference on Vascular Targeting:

Meeting overview"
CANCER RESEARCH 01 MAR 2003 UNITED STATES, vol. 63, no. 5, 1 March 2003 (2003-03-01), pages 1144-1147, XP002342602 ISSN: 0008-5472

D3: HALIN C ET AL: "Enhancement of the antitumor activity of interleukin-12 by targeted delivery to neovasculature"
NATURE BIOTECHNOLOGY, NATURE PUBLISHING, US, vol. 20, no. 3, March 2002 (2002-03), pages 264-269, XP002256784 ISSN: 1087-0156

D4: WO 03/093478 A (MOLMED SPA; CORTI, ANGELO; CURNIS, FLAVIO) 13 November 2003 (2003-11-13)

D5: HUANG X ET AL: "TUMOR INFARCTION IN MICE BY ANTIBODY-DIRECTED TARGETING OF TISSUE FACTOR TO TUMOR VASCULATURE"
SCIENCE, AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE,, US, vol. 275, 24 January 1997 (1997-01-24), pages 547-550, XP002071588 ISSN: 0036-8075

D6: VAN VLIET A I ET AL: "Distribution of fibronectin isoforms in human renal disease"
JOURNAL OF PATHOLOGY 2001 UNITED KINGDOM, vol. 193, no. 2, 2001, pages 256-262, XP002342603 ISSN: 0022-3417

D7: VITI F ET AL: "Increased binding affinity and valence of recombinant antibody fragments lead to improved targeting of tumoral angiogenesis"
CANCER RESEARCH 15 JAN 1999 UNITED STATES, vol. 59, no. 2, 15 January 1999 (1999-01-15), pages 347-352, XP002124782 ISSN: 0008-5472

D8: CARNEMOLLA B ET AL: "A tumor-associated fibronectin isoform generated by alternative splicing of messenger RNA precursors"
JOURNAL OF CELL BIOLOGY 1989 UNITED STATES, vol. 108, no. 3, 1989, pages 1139-1148, XP002342604 ISSN: 0021-9525

D9: ZHU Z ET AL: "INHIBITION OF TUMOR GROWTH AND METASTASIS BY TARGETING TUMOR-ASSOCIATED ANGIOGENESIS WITH ANTAGONISTS TO THE RECEPTORS OF VASCULAR ENDOTHELIAL GROWTH FACTOR"
INVESTIGATIONAL NEW DRUGS, MARTINUS NIJHOFF PUBLISHERS, BOSTON, US, vol. 17, no. 3, 1999, pages 195-212, XP000940444 ISSN: 0167-6997

D10: PENG L S ET AL: "Mechanism of antitumor activity of a single-chain

interleukin-12 IgG3 antibody fusion protein (mscIL-12.her2.IgG3)" JOURNAL OF INTERFERON AND CYTOKINE RESEARCH, vol. 21, no. 9, 2001, pages 709-720, XP002342605 ISSN: 1079-9907

D11: LADELL KRISTIN ET AL: "A combination of plasmid DNAs encoding murine fetal liver kinase 1 extracellular domain, murine interleukin-12, and murine interferon-gamma inducible protein-10 leads to tumor regression and survival in melanoma-bearing mice." JOURNAL OF MOLECULAR MEDICINE (BERLIN), vol. 81, no. 4, April 2003 (2003-04), pages 271-278, XP002342606 ISSN: 0946-2716

D12: DICKERSON ERIN B ET AL: "Development of an IL-12 fusion protein for molecular targeting of tumor vasculature" PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL MEETING, no. 41, March 2000 (2000-03), page 798, ABSTRACT NO. 5074, XP002342607 & 91ST ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH.; SAN FRANCISCO, CALIFORNIA, USA; APRIL 01-05, 2000 ISSN: 0197-016X

D13: WO 02/02143 A (LEXIGEN PHARMACEUTICALS CORP) 10 January 2002 (2002-01-10)

D14: WO 99/29732 A (LEXIGEN PHARMACEUTICALS CORPORATION) 17 June 1999 (1999-06-17)

D15: MAJEWSKI S ET AL: "INTERLEUKIN-12 INHIBITS ANGIOGENESIS INDUCED BY HUMAN TUMOR CELL LINES IN VIVO" JOURNAL OF INVESTIGATIVE DERMATOLOGY, NEW YORK, NY, US, vol. 106, no. 5, 1996, pages 1114-1118, XP000949299 ISSN: 0022-202X

2 Invention 1

Document **D1** discloses tumour targeting using the fusion protein of L19 with IL-12
Document **D2** discloses tumour targeting using the fusion protein of L19 with IL-12
Document **D3** discloses a fusion protein of anti-oncofoetal fibronectin with IL-12, and its efficacy in the treatment of tumours. This conjugate seems excluded in claims 1-33, but not in claim 34.
Document **D4** discloses on page 26, line 24 of the table, the combination IL-12 +

anti-oncofetal fibronectin is mentioned as one of the preferred combinations.
Document **D5** discloses the targeting of IL-12 to the vasculature using a bispecific antibody. Like in the present application, the result is the infarction of the tumour.
Document **D6** discloses the isoforms of fibronectin targeted by BC-1.
Document **D7** discloses 2 antibodies targeting ED-B: E1 et L19.
Document **D8** discloses the specificity of antibody BC-1.
Document **D9** discloses the use of anti-oncofoetal fibronectin antibodies in the anti-angiogenic treatment of tumours.
Document **D10** discloses the fusion protein of anti-her2 variable region with IL-12, and its anti-cancer effects. The passage on page 715 describes the antiangiogenic effect of the conjugate.
Document **D11** discloses a fusion protein containing IL-12, targeted using the VEGF receptor.
Document **D12** discloses a different way of targeting IL-12 to the vasculature. The resulting effect is, however, the same as in the present application.
Document **D13** discloses the use of a conjugate of IL-12 with a different antibody. It also mentions therapy in combination with other anti-cancer agents.
Document **D14** was cited by the applicant in support of the preparation of the fusion protein. Example 6 describes the Pharmacokinetic Properties of IL-12 Fusion Proteins. The antibody-IL-12 fusion proteins were tested for their pharmacokinetic behaviour following intravenous injection into Balb/c mice. Example 7: Treatment of established colon carcinoma with antibody-IL-12 fusion protein.

Due to its general wording, present claim 34 seems to be anticipated by the description of the fusion proteins described in each of documents **D1** to **D4**. As a consequence, this claim does not meet the requirements of Article 33.2 PCT for novelty.

The fusion proteins defined in present claims 1-33 can be distinguished from the fusion proteins as described in any of **D1** to **D4** by their exact sequence.
The problem to be solved by these different fusion proteins is, again identical: treatment of solid tumours by targeting IL-12 to the neovasculature.
This problem is known to be solved in many ways. Where **D1** to **D4** use the antibody L19 for targeting oncofoetal fibronectin, **D5** uses a bispecific antibody, and **D9** another antibody.

Antibodies targeting other epitopes are also used for targeting IL-12 to tumours. The antibody used in **D10** targets a tumour-specific antigen. In **D11**, VEGF is the target. In **D12**, a small peptide targeting $\alpha_V\beta_3$ is used to bring IL-12 to the vasculature.
Documents **D6** and **D8** describe the antibody BC-1, used in the present application. Like L19, it targets specifically oncofoetal fibronectin. The only difference between documents **D1** to **D4** and the present application is therefore the act, that the targeting antibody has affinity for a different portion of the same oncofoetal fibronectin.

Throughout the present application, the difference between targeted and non-targeted IL-12 is shown. The present authority can therefore not determine any effect resulting from the different way of targeting the same antigen. The conclusion can therefore only be, that targeting IL-12 to oncofoetal fibronectin does indeed result in more efficient tumour infarction than the use of non-targeted IL-12, but that this result is known from each of **D1** to **D4**. As a consequence, this targeting fusion protein, insofar as novel, does not meet the requirements of Article 33.3 PCT for inventive step.

Inventions 2 and 3.

Inventions 2 and 3 as defined above relate to a method of preparing the different compounds defined in claims 1-34 (claim 42), and to the different types of products (nucleic acids, expression vector and host cell) necessary for this method (claims 35-41).
Document **D14** was cited by the applicant in support of the preparation of the fusion protein. Example 4 describes the Expression of antibody-IL-12 Fusion Proteins, Example 5 the Expression of Single Chain IL-12 Fusion Proteins.
Due to its general wording, present claim 25 is anticipated by this document.
Present inventions 2 and 3 can be distinguished from the teachings of **D14** by the fact, that the exact sequence used is different. However, it is is standard practice for the person skilled in the art to adapt the nucleic acid sequence to the protein (s)he wishes to obtain. Therefore, present claims 36-41 do not meet the requirement of Article 33.3 PCT for inventive step.

DEPENDENT CLAIMS

The dependent claims do not contain any features which, in combination with the features

of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step (Article 33(2) and (3) PCT).

For the assessment of the present claim 47 on the question whether it is it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognise as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII
Certain observations on the international application

Claims 1-50 do not meet the requirements of Article 6 PCT in that the matter for which protection it is sought it is not clearly defined. The claims attempt to define the subject-matter in terms of the result to be achieved, which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result.

Claims 51-52 do not define the matter for which protection is sought in technical terms, and therefore fail to meet the requirements of Article 6 PCT for clarity.